CHAPTER 3a

A different approach to breast-feeding of the infant with Phenylketonuria

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Eur J Pediatr (2003) 162: 323-326
Parts of this article have been published before in the "Tijdschrift voor Kindergeneeskunde" 2002; 70:5 195-9.

ABSTRACT:

We studied the possibility and safety of a new approach to breast-feeding infants with Phenylketonuria (PKU). We compared a group of PKU infants being breast-fed according to our new protocol to a group of PKU infants receiving formula only. The breast-fed group consisted of 9 infants born between 1994 and 1999 being breast-fed at the moment of diagnosis. The formula fed group consisted of 9 PKU infants, born between 1988 and 1997. In the breast-fed group feedings alternated between breast-feeding and Phenylalanine (Phe) free bottle-feeding. The numbers of breast-feedings were adapted to the plasma Phe concentrations. At each feeding, bottle- or breast-feeding, the child was allowed to drink till satiety. Data about metabolic control and growth during the first 6 months showed no statistically different results. The mean Phe concentration in the breast fed group was 170 μmol /l (range 137-243) and in the formula fed group 181 μmol/l (range 114-257). Compared to a routine where both bottle and breast are offered at each feeding, this new approach is more convenient for the parents and the child will be able to empty the breast, therefore drinking not only foremilk but also hindmilk. *Conclusion:* The results suggest that this feeding protocol is safe in the strict treatment of otherwise healthy infants with phenylketonuria.

INTRODUCTION

Breast-feeding infants with Phenylketonuria (PKU) has long been uncommon in the Netherlands. Recent data showed that of 97 PKU infants being breast-fed at the moment of diagnosis, only 4 continued to be breast-fed after diagnosis (Crone M.R personal communication). Parents of infants with PKU were advised to switch to bottle-feeding after diagnosis. However promotion of breast-feeding is in accordance to the WHO/UNICEF recommendation[15]. General advantages such as the content of long chain polyunsaturated fatty acids[18], immunoglobulins, better absorbtion of iron[9], non protein nitrogen combinations such as lactoferrin, polyamines and nucleotides [3], as well as advantages in emotional attachment and satisfaction are also applicable to the PKU infant.

Mothers, who have to stop breast-feeding abruptly at the time of PKU diagnosis, may experience extra feelings of guilt, making acceptance even more difficult[9]. Another advantage of breast-feeding in PKU is the low amount of Phenylalanine (Phe) in human milk in comparison to standard infant formulas, which makes it possible to give more human milk than standard formula.

Until now, two different guidelines have been described for breast-feeding PKU infants. One is based on the exact measurement of the intake of breast-milk by measuring expressed breast-milk or performing weight checks of the children before and after feeding[1]. The other guideline advises to start each feed with a measured amount of Phe free formula followed by breastfeeding till satiety[4,6,10,11]. Both guidelines have emotional and practical disadvantages in stimulating breast-milk production.

The aim of this study was to investigate the possibility of breast-feeding PKU infants with a set number of breast-feedings per day in a fixed schedule alternated with Phe-free formula. The amount of breast-milk was not controlled by weight checks. We retrospectively compared a group of PKU infants entirely formula-fed with a group of

PKU infants having been breast-fed according to our protocol.

SUBJECTS AND METHODS

Subjects:

All patients were diagnosed with PKU by neonatal screening and treated in the University Hospital of Groningen. From 1994 till 1999 the continuation of breast-feeding was offered to nine new-born babies breast-fed until diagnosis. The fully formula-fed group was born between 1988 and 1997. This group included infants born before breast-feeding was recommended and infants who were bottle-fed at the time of diagnosis. The patient characteristics of both groups are presented in table 1 and are not significantly different with one exception. Median age at diagnosis in the control group was significantly higher without a difference in Phe concentration at time of diagnosis. The difference in median age at time of diagnosis was due in part to the fact that the fully bottle-fed patients were diagnosed between 1988 and 1994. In this

Table 1. Baseline patient characteristics. *

	Breast fed (n=9)	Formula fed (n=9)	Significance†
Age at diagnosis (days)	7(6/8)	12(9/16)	<0.01**
Phe at diagnosis ‡ (µmol/l)	1600(390/2200)	780(200/4150)	0.44
Length (z-score) §	-0.38(-0.45/0.24)	0.07(-1.26/1.79)	0.09
Weight (z-score) §	-0.52(-1.37/0.65)	-.33(-1.79/3.11)	1.00
Headcircumference (z-score) §	-0.20(-0.99/0.96)	0.57(-1.36/2.70)	0.34
Sexe	2♂:7♀	5♂:4♀	-
Ethnicity			
Dutch	5	8	-
Turkish	3	1	-
Georgian	1	0	-
Duration of breastfeeding (weeks)	10(7-33)	-	-
Maternal Phe ‡	114(96-172)	143(91-153)	0.6

* numbers represent median values, ranges min/max are given in parentheses

† p-value resulting from Mann-Whitney test for difference in medians

‡ Phe = plasma phenylalanine concentration in µmol/l

§ 0-1 month of age

period the heel puncture was performed between days 7 and 9 after birth. In 1994 this has changed to days 5 and 7, and referral to our centre occurred a few days earlier[16]. In the bottle-fed group we also found two patients with a dubious first screening test and a delayed diagnosis. In the other group we found only one such patient.

We measured the Phe concentrations of the mothers in both groups.

Feeding method:

The feeding schedule for the breast-fed group was based on alternating breast-feeding and Phe free bottle- feeding, resulting in individual schedules for each child depending on tolerance and age. The first few days after diagnosis the mother usually breast-fed the infant once daily, the numbers of breast-feedings increased over the following days monitoring the plasma Phe concentrations daily. The mother expressed breast-milk a few times a day as long as the infant was allowed to drink breast-feeding only once or twice during the first few days, to stimulate milk production. Bottle- and breast-feeding were divided equally throughout the day and advice was given to keep the same sequence. At all feedings, either bottle or breast, the child was allowed to drink until satiated.

The completely bottle-fed group was fed as usual with a Phe free formula mixed together with a standard formula. The amount of both formulas was adjusted to obtain plasma Phe concentrations within the therapeutic range.

Metabolic control and growth:

The frequency of measuring plasma Phe concentrations was gradually reduced from daily in the first week after diagnosis, to twice a week, weekly and biweekly when levels were stable within the therapeutically aimed range. We studied the length of time needed for the plasma Phe concentrations to reach the therapeutically aimed range (120 to 360 μmol/l) after diagnosis. The Phe concentrations of the first 6 months were plotted in order to track the Phe concentrations were within the aimed range (<360 and >120 μmol/l), above the aimed range (>360 μmol/l), or below the aimed range (<120μmol/l). Phe concentrations were determined in plasma using an amino acid analyser with a coefficient of variation of 2%.

Growth (weight, length and head circumference) was followed from the time of diagnosis until 6 months of age. The results were expressed as individual z-scores according to the latest Dutch Growth diagrams[14]. Statistical analysis was performed using the non- parametric Mann-Whitney-test.

RESULTS

Table 2 presents the data concerning the metabolic control showing that the time to stabilise Phe values and further metabolic control was not different between the two groups.

Table 3 shows that z-scores for growth were satisfactory and statistically not different in both groups. The data of the headcircumference of both groups are further presented in Figure 1. At the start the headcircumference in the bottle-fed group was

Table 2. Metabolic control in breast fed and formula fed PKU patients during the first 6 months of life. *

	Breast fed (n=9)	Formula fed (n=9)	Significance†
Mean Phe ‡ (µmol/l)	170(137-243)	181(114-257)	0.86
Variation coefficient of mean Phe (%)	69(34-139)	66(31-119)	0.93
% Phe <120 µmol/l §	31(5-65)	26(2-65)	0.61
% Phe 120-360 µmol/l ‖	56(20-90)	59(22-98)	0.67
% Phe > 360 µmol/l ¶	6(1-25)	4(0-37)	0.49
Days until Phe 120-360 µmol/l	6(2-15)	6(0-26)	0.80

* numbers represent median values, ranges min/max are given in parentheses
† resulting from Mann-Whitney test for difference in medians
‡ Phe = plasma phenylalanine concentration
§ percentage of time in which plasma phenylalanine concentration was below the specified range
‖ percentage of time in which plasma phenylalanine concentrations were within the specified range
¶ percentage of time in which plasma phenylalanine concentrations were above the specified range

Table 3. Growth in breast-fed and formula-fed PKU patients during the first 6 months of life. *

	Breast fed (n=9)	Formula fed (n=9)	Significance †
Length			
0-1 month	-0.38(-1.45/0.24)	0.07(-1.26/1.79)	0.09
3-4 months	0.48(-0.66/-1.48)	0.17(-0.66/1.62)	0.80
6-7 months	0.33(-0.98/2.42)	0.68(-0.11/2.43)	0.34
Weight			
0-1 month	-0.52(-1.37/0.65)	-0.33(-1.79/3.11)	1.00
3-4 months	0.35(-1.72/1.34)	0.57(-0.56/1.51)	0.34
6-7 months	0.30(-1.46/2.16)	0.51(-0.12/2.44)	0.34
Headcircumference			
0-1 month	-0.20(-0.99/0.96)	0.57(-1.36/2.70)	0.34
3-4 months	-0.01(-1.32/0.57)	0.78(-1.66/2.03)	0.09
6-7 months	-0.15(-1.54/0.36)	0.87(-1.70/2.19)	0.11

* numbers represent median Z-scores, ranges min/max are given in parentheses
† resulting from Mann-Whitney test for difference in medians

larger than in the breast-feeding group. The difference remained but never reached statistical difference. The results of the Phe concentrations of the mothers show that none of the mothers had hyperphenylalaninaemia.

All nine mothers who breast-fed their child at the moment of diagnosis wanted to continue breast-feeding and were very positive afterwards. In three patients it was necessary to implement one "mixed" feeding (combination of Phe- free bottle-feeding and breast-feeding), when the switch to one total breast- or bottle-feeding resulted in too high or too low plasma Phe concentrations. At 4 weeks of age the number of breast-feedings in all the children was 50 % or more of their total amount of feedings. We did not see any problems of nipple- bottle confusion in the babies.

DISCUSSION

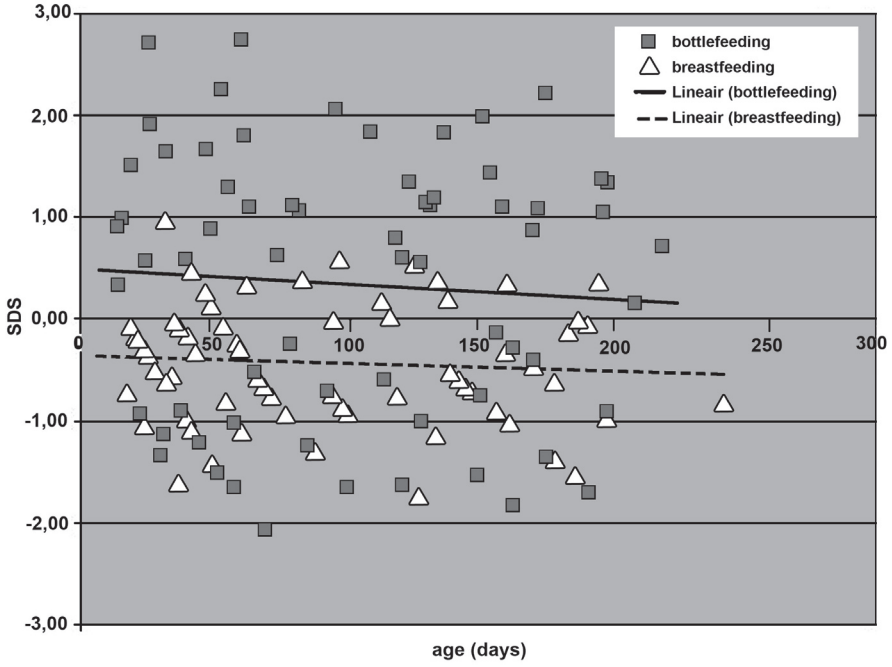

Figure 1. Headcircumference of both groups.

For a long time we have assumed that it is not safe to breast-feed the newly diagnosed PKU infant without monitoring the amount of human milk by weighing the expressed milk or by weighing the baby before and after drinking. Giving a certain amount of Phe free bottle-feed followed by "breast-feeding ad lib" in each feeding was an improvement[4,6,10,11]. This way the satiety controls the amount of breast-feeding.

In our study we investigated further the possibility and safety of alternating Phe free bottle-feedings and breast-feedings. In 1986 MacCabe described this feeding method

in order to improve iron-absorption[9]. In our feeding protocol the breast-feeding was fixed in the total number of breast-feeds per day and in the alternating sequence throughout the day. The child was allowed to drink till satiety both by bottle- and breast-feeding. The purpose of the study was to determine whether good metabolic control could be achieved and maintained in this feeding-schedule. Although the number of patients is relatively small, data showed that applying our breast-feeding protocol to otherwise healthy PKU patients, the Phe concentrations could be kept within the therapeutic range.

The breast-fed group showed a growth comparable to the bottle-fed group and better when compared to the average Dutch PKU population[16]. The differences in head circumference between both groups could not be explained by differences in the Phe concentration of the mothers.

The difference in age at diagnosis might be expected to induce higher Phe concentrations in the bottle-fed group. In contrast there was some tendency of higher plasma Phe concentrations in the breast-fed group indicating that the breast-fed group certainly did not have a less severe phenylalanine hydroxylase deficiency.

Median duration of breast-feeding was 10 weeks (range 7 to 33 weeks), which is comparable to the normal Dutch population[2]. The reasons to stop breast-feeding, such as returning to work, stress in family circumstances and lack of milk- production did not seem different from the average in the Dutch population.

Our data further suggests that continuing breast-feeding may have a positive influence on the emotional acceptance by the parents. The emotional advantages were already mentioned by McCabe[9]. Especially the fact that the mother did not have to stop her breast-feeding abruptly is a positive factor in acceptance of the PKU diagnosis.

This study did not investigate the 24- hour fluctuation in plasma Phe concentration. At present, little is known about this daily variation of Phe concentrations in PKU infants younger than one year of age. Both the studies of Macdonald et al and van Spronsen et al concern PKU patients older than one year[7,8,12,13]. The study of Gerdes et al supplies us only with two Phe concentrations during a short time span of the day[5]. It might be hypothesised that supplying such young PKU infants with a rather unbalanced daily distribution of the natural protein and the Phe free formula may result in large daily fluctuations of plasma Phe concentrations. The high feedings-frequency in young infants however will reduce this effect. Future studies should also address the diurnal Phe variations both in case of breast-feeding and formula feeding.

Results of this study suggest that breast-feeding in PKU using our protocol is technically possible. With respect to the growth and metabolic control the protocol appears safe. With respect to the metabolic control in PKU infants, future studies are necessary on the use of breast-milk and formula. We hope that our more convenient breast-feeding method may result into a higher percentage of breast-fed PKU infants, and thus will contribute to the emotional acceptance by the parents and an optimal development of the PKU infant.

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